PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MJL/B45308		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/06094	10.06.2003	13.06.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K39/00		
Applicant		
GLAXOSMITHKLINE BIOLOGICALS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.12.2003	29.11.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06094

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-25 as originally filed

Claims, Numbers

14-19 as originally filed

1-13 received on 16.11.2004 with letter of 16.11.2004

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12

because:

☒ the said international application, or the said claims Nos. 12 (concerning industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11, 13
	No:	Claims	c.f. separate sheet

2. Citations and explanations

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06094

see separate sheet

item III

1 **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability (Rule 67.1, PCT)**

For the assessment of present **claim 12** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claim 12 relates to subject matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv), PCT**. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims **(Article 34(4)(a)(I), PCT)**.

item V

2 The following documents have been cited in the present written opinion; the numbering will be adhered to in the rest of the procedure:

D1 WO 02 09643 A (GRANOFF DAN ;MOE GREGORY R (US); CHILDREN S HOSPITAL OAKLAND RE (U) 7 February 2002 (2002-02-07) cited in the application

D2 Moe-GR et al. (1999) Differences in surface expression of NspA among Neisseria meningitidis group B strains. Infection and Immunity 67(11): 5664-5675.

D3 WO 01 09350 A (DALEMANS WILFRIED L J ;SMITHKLINE BEECHAM BIOLOG (BE); THIRY GEORG) 8 February 2001 (2001-02-08) cited in the application

3 Novelty (Art. 33(2), PCT)

3.1 It would appear that no documents are comprised in the known prior art explicitly disclosing the subject matter of **claims 1-13**, therefore, these claims would appear to be novel in the sense of **Article 33(2), PCT**.

4 Inventive step (Art. 33(3), PCT)

D1 is considered to be the closest prior art and discloses a method for eliciting broad spectrum protective immunity against Neisseria meningitidis comprising the steps: 1) administering a 1st microvesicle preparation (OMV or MV or both together) from a 1st serosubtype; 2) administering a 2nd OMV/MV prep. from a 2nd serosubtype (different from serosubtype 1) and evtl. 3) a 3rd OMV/MV serotype or serosubtype prep. Administrations can be serially or as a mixture (claims 1, 5, 7 10, 14-16, 29). In case that the strains used to produce MV/OMV are associated with endotoxin or particular high

levels of endotoxin the MV/OMV are optionally treated to reduce endotoxin. (p 19, l 15 - 17). **D1** notes that the SBA response to OMV vaccines tends to be strain specific. PorA being immunodominant and the immunity induced is predominantly specific to the strains from which the membrane vesicles were obtained. Accordingly, this limitation is primarily because of antigenic variability of the PorA protein. The method disclosed in **D1** should circumvent the problem of immunodominance or antigenically variable domains of PorA in vesicle- or PorA-based vaccines by focussing the Ab response on common Ag in the vaccine strains. The method induces SBA against Neisseria serosubtypes that were not used in the vaccine preparation. This should be due to the fact that the method induces Ab that are specific for both, conserved and non-conserved Ag (p 14, l 24 - p 15, l 12). Accordingly, an important aspect of **D1** is that the Ag composition used to prime and boost protective immunity are prepared from strains of Neisseria that possess variant immunodominant antigens (e.g. PorA, PorB, NsPA, pilin etc) (p 27, l 4 - 11).
This approach also has broad applicability for vaccination against Neisseria meningitidis strains representative of other serogroups such as A, C, Y, or W-135, and also against other members of the genus Neisseria. **D1** cites a publication by Moe-GR et al (c.f. **D2** p 42, l 23-24) listing different NspA positive group B strains, amongst others CU385, H44/76 and others (c.f. Table 1).

The subject matter of **claim 1** differs from **D1** in that it claims a multivalent meningococcal bleb composition comprising a bleb preparation deficient in PorA in that it has less than 80% of the amount of PorA as compared to the same quantity of blebs made from strain H44/76 and a bleb preparation that is not deficient in PorA compared to blebs made from strain H44/76.
The technical problem is to provide an improved meningococcal vaccine providing protection against homologous but also heterologous meningococcal strains.
The claimed solution is the use of a multivalent meningococcal bleb composition comprising a bleb preparation deficient in PorA in that it has less than 80% of the amount of PorA as compared to the same quantity of blebs made from strain H44/76 and a bleb preparation that is not deficient in PorA compared to blebs made from strain H44/76.

Although the closest prior art (**D1**) contains some vague statements that the problem of immunodominance of antigenically variable domains of PorA in vesicle- or PorA-based vaccines can be circumvented by focussing the Ab response on common Ag in the vaccine strains, **D1** does not provide any hint towards the use of strains with specific PorA %-ages.
Moreover, the experimental data filed with letter of 23.08.2003, show that a

meningococcal bleb preparation according to **claim 1** (i.e. comprising two different strains with "high" and "low" PorA expression relative to the H44/76 strain) leads to immune responses against homologous and heterologous meningococcal strains,
It would not appear that such a specific bleb preparation would have been derivable from the prior art.
Thus, the subject matter of **claims 1-5** would appear to involve an inventive step in the sense of **Art. 33(3), PCT**.
Consequently also the subject matter of **claims 6-13** would also appear to involve an inventive step in the sense of **Art. 33(3), PCT**.

5 further remarks

5.1 The vague statement in the description on page 21, line 5 (non-limiting) implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (**Article 6 PCT**) when used to interpret them (see also the **PCT Guidelines, III-4.3a**).

5.2 In a later European regional phase objections might be raised against any expression within the description such as "...incorporated by reference..." (e.g. on page 3, line 13-15) as the regional patent law requires that the application is self-contained.

5.3 In a later European regional phase also the description would have to be adapted to the amended set of claims.

We Claim:

1. A multivalent meningococcal bleb composition comprising at least one bleb with homologous bactericidal activity which is derived from a meningococcal strain with a serosubtype that is prevalent in a country of use, and at least one bleb with heterologous bactericidal activity which is derived from a meningococcal strain which need not have a serosubtype that is prevalent in the country of use.

2. The multivalent meningococcal bleb composition of claim 1 wherein the bleb with heterologous bactericidal activity is deficient in an immunodominant outer membrane protein compared to blebs derived from wild-type strain H44/76, and the bleb with homologous bactericidal activity is not deficient in said immunodominant outer membrane protein compared to blebs derived from wild-type strain H44/76.

3. The multivalent meningococcal bleb composition of claim 2 wherein the bleb with heterologous bactericidal activity is derived from a wild-type meningococcal strain that is naturally deficient in said immunodominant outer membrane protein.

4. The multivalent meningococcal bleb composition of claim 2 wherein the bleb with heterologous bactericidal activity is derived from a genetically-engineered meningococcal strain that produces less or none of said immunodominant outer membrane protein compared to the wild-type strain.

5. The multivalent meningococcal bleb composition of claim 4 wherein said genetically-engineered meningococcal strain has been genetically altered in either the promoter or coding region of the gene encoding the immunodominant outer membrane protein such that the strain produces less or none of said immunodominant outer membrane protein.

6. The multivalent meningococcal bleb composition of claims 2-5 wherein the immunodominant outer membrane protein is PorA.

optionally comprises further blebs with homologous bactericidal activity derived from one or more meningococcal strains with serosubtypes selected from the following list: P1.7,1 ; P1.5,2 ; P1.22a,14 ; and P1.14.

16. The vaccine of claim 12 or 13 suitable for use in Norway wherein the bleb with homologous bactericidal activity or the bleb preparation that is not deficient in PorA is derived from a meningococcal strain with a serosubtype of P1.16.

17. A method of manufacturing the multivalent meningococcal bleb composition of claims 1-11 or the vaccine of claims 12-16 comprising the step of combining the bleb with homologous bactericidal activity with the bleb with heterologous bactericidal activity, or the step of combining the bleb preparation that is not deficient in PorA with the bleb preparation that is deficient in PorA.

18. A method of preventing or treating neisserial, preferably meningococcal, disease comprising the step of administering an immunologically effective amount of the vaccine of claims 12-16 to a host in need thereof.

19. The use of an immunologically effective amount of the vaccine of claims 12-16 in the manufacuture of a medicament for the prevention or treatment of neisserial, preferably meningococcal, disease.

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